Heart Muscle Microphysiological System for Cardiac Liability Prediction of Repurposed COVID-19 Therapeutics.

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Authors: Berenice Charrez, Verena Charwat, Brian A Siemons, Ishan Goswami, Courtney Sakolish, Yu-Syuan Luo, Henrik Finsberg, Andrew G Edwards, Evan W Miller, Ivan Rusyn, Kevin E Healy

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Public Summary:
We report on a preclinical drug screening platform, a cardiac microphysiological system (MPS), to rapidly identify clinically relevant cardiac toxicity associated with drugs to treat COVID-19. The cardiac MPS is a microfabricated fluidic system in which cardiomyocytes (heart cells) derived from human induced pluripotent stem cells self-arrange into a beating tissue that mimic human heart muscle. The cardiac MPS rapidly determined the cardiac safety of potential COVID-19 therapeutics, ultimately accelerating patients' access to safe and effective treatments.

Scientific Abstract:
Despite global efforts, it took 7 months between the proclamation of global SARS-CoV-2 pandemic and the first FDA-approved treatment for COVID-19. During this timeframe, clinicians focused their efforts on repurposing drugs, such as hydroxychloroquine (HCQ) or azithromycin (AZM) to treat hospitalized COVID-19 patients. While clinical trials are time-consuming, the exponential increase in hospitalizations compelled the FDA to grant an emergency use authorization for HCQ and AZM as treatment for COVID-19, although there was limited evidence of their combined efficacy and safety. The authorization was revoked 4 months later, giving rise to controversial political and scientific debates illustrating important challenges such as premature authorization of potentially ineffective or unsafe therapeutics, while diverting resources from screening of effective drugs. Here we report on a preclinical drug screening platform, a cardiac microphysiological system (MPS), to rapidly identify clinically relevant cardiac liabilities associated with HCQ and AZM. The cardiac MPS is a microfabricated fluidic system in which cardiomyocytes derived from human induced pluripotent stem cells self-arrange into a uniaxially beating tissue. The drug response was measured using outputs that correlate with clinical measurements such as action potential duration (proxy for clinical QT interval) and drug-biomarker pairing. The cardiac MPS predicted clinical arrhythmias associated with QT prolongation and rhythm instabilities in tissues treated with HCQ. We found no change in QT interval upon acute exposure to AZM, while still observing a significant increase in arrhythmic events. These results suggest that this MPS can not only predict arrhythmias, but it can also identify arrhythmias even when QT prolongation is absent. When exposed to HCQ and AZM polytherapy, this MPS faithfully reflected clinical findings, in that the combination of drugs synergistically increased QT interval when compared to single drug exposure, while not worsening the overall frequency of arrhythmic events. The high content cardiac MPS can rapidly evaluate the cardiac safety of potential therapeutics, ultimately accelerating patients' access to safe and effective treatments.